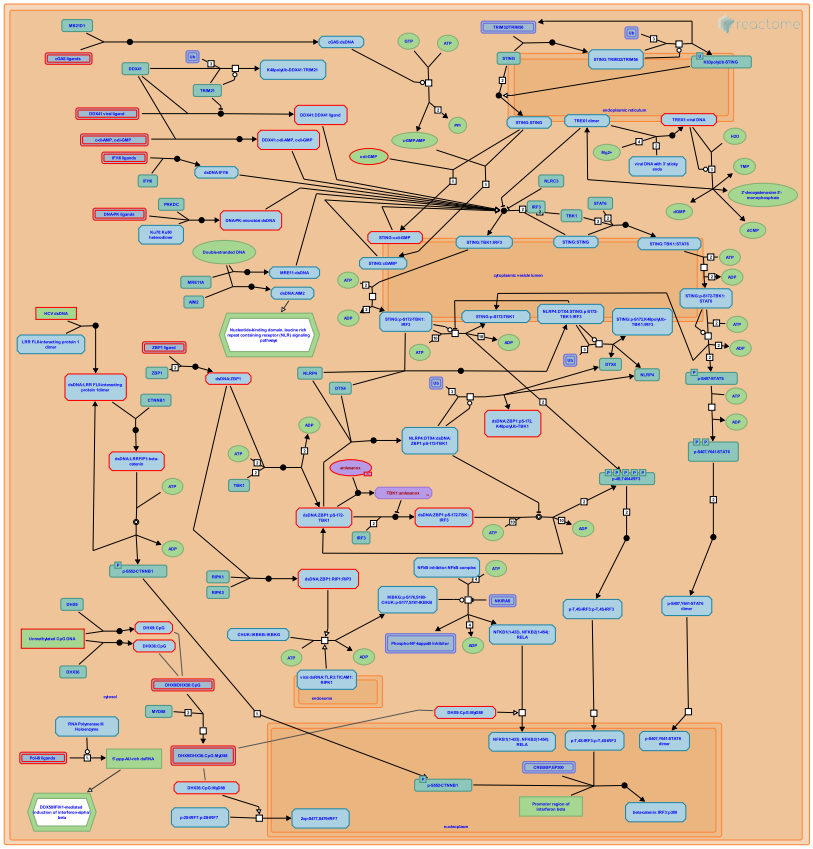
Cytosolic sensors of pathogen-associated DNA



D'Eustachio, P., Jin, L., Jupe, S., Kufer, TA., Mocarski, ES., Rittinger, K., Shamovsky, V., Upton, JW., Wong, E., Wu, J.

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

19/05/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

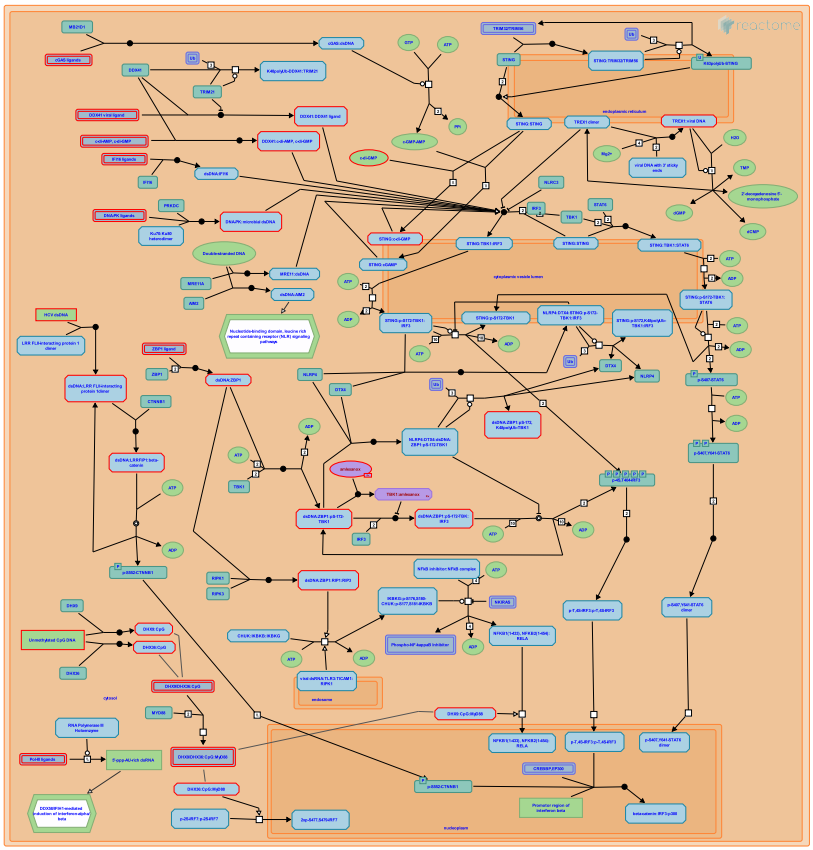
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 6 pathways and 4 reactions (see Table of Contents)

Cytosolic sensors of pathogen-associated DNA

Stable identifier: R-HSA-1834949



Presence of pathogen-associated DNA in cytosol induces type I IFN production. Several intracellular receptors have been implicated to some degree. These include DNA-dependent activator of interferon (IFN)-regulatory factors (DAI) (also called Z-DNA-binding protein 1, ZBP1), absent in melanoma 2 (AIM2), RNA polymerase III (Pol III), IFN-inducible protein IFI16, leucine-rich repeat flightless interacting protein-1 (LRRFIP1), DEAH-box helicases (DHX9 and DHX36), DEAD-box helicase DDX41, meiotic recombination 11 homolog A (MRE11), DNA-dependent protein kinase (DNA-PK), cyclic GMP-AMP synthase (cGAS) and stimulator of interferon genes (STING).

Detection of cytosolic DNA requires multiple and possibly redundant sensors leading to activation of the transcription factor NF-kappaB and TBK1-mediated phosphorylation of the transcription factor IRF3. Cytosolic DNA also activates caspase-1-dependent maturation of the pro-inflammatory cytokines interleukin IL-1beta and IL-18. This pathway is mediated by AIM2.

Literature references

Bowie, AG., Paludan, SR. (2013). Immune Sensing of DNA. *Immunity, 38*, 870-880.

Fitzgerald, KA., Sharma, S. (2011). Innate immune sensing of DNA. *PLoS Pathog, 7*, e1001310.

Deddouche, S., Goubau, D., Reis e Sousa, C. (2013). Cytosolic Sensing of Viruses. *Immunity, 38*, 855-869.

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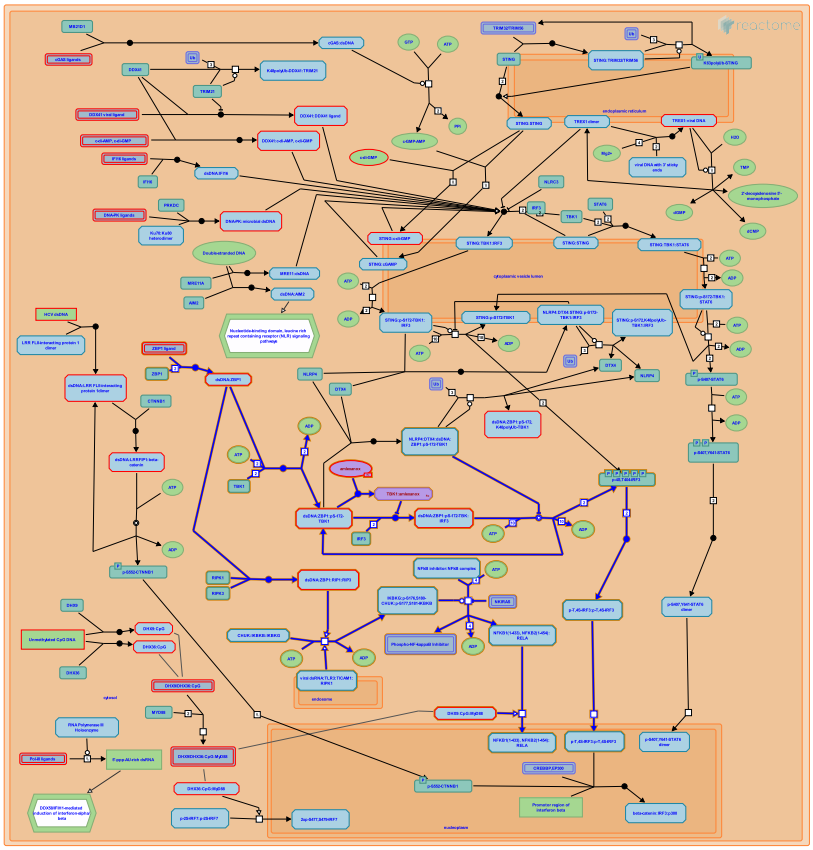
ZBP1(DAI) mediated induction of type I IFNs ↗

Location: Cytosolic sensors of pathogen-associated DNA

Stable identifier: R-HSA-1606322



Z-DNA-binding protein-1 (ZBP1), also known as, DNA-dependent activator of IFN-regulatory factors (DAI) was reported to initiate innate immune responses in murine L929 cells upon stimulation by multiple types of exogenously added DNA (Takaoka A et al 2007). Human cytomegalovirus (HCMV) was shown to stimulate ZBP1-mediated induction of IRF3 in human foreskin (DeFilippis VR et al 2010). ZBP1 was also implicated in activation of NF-kappaB pathways in human embryonic kidney HEK293T cells (Kaiser WJ et al 2008, Rebsamen M et al 2009). However, the role and importance ofZBP1 as dsDNA sensor remain controversial, since knocking down ZBP1 expression in other human or murine cell types by siRNA had very little effect on cellular responses to cytosolic DNA, suggesting the presence of alternative pathway (Wang ZC et al 2008, Lippmann J et al 2008). Tissue-specific expression of human ZBP1 also suggests that ZBP1 may function in cell-type specific way (Rothenburg S et al 2002).

Literature references

Haag, F., Schwartz, T., Koch-Nolte, F., Rothenburg, S. (2002). Complex regulation of the human gene for the Z-DNA binding protein DLM-1. *Nucleic Acids Res, 30*, 993-1000. ↗

Mocarski, ES., Kaiser, WJ., Upton, JW. (2008). Receptor-interacting protein homotypic interaction motif-dependent control of NF-kappa B activation via the DNA-dependent activator of IFN regulatory factors. *J Immunol, 181*, 6427-34. ↗

Lu, Y., Tamura, T., Choi, MK., Ban, T., Yanai, H., Wang, Z. et al. (2008). Regulation of innate immune responses by DAI (DLM-1/ZBP1) and other DNA-sensing molecules. *Proc Natl Acad Sci U S A, 105*, 5477-82. ↗

Benedict, CA., Rebsamen, M., Vazquez, J., Hofmann, K., Michallet, MC., Schroder, K. et al. (2009). DAI/ZBP1 recruits RIP1 and RIP3 through RIP homotypic interaction motifs to activate NF-kappaB. *EMBO Rep, 10*, 916-22. ↗

Lu, Y., Choi, MK., Ohba, Y., Ban, T., Miyagishi, M., Yanai, H. et al. (2007). DAI (DLM-1/ZBP1) is a cytosolic DNA sensor and an activator of innate immune response. *Nature, 448*, 501-5. ↗

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STING mediated induction of host immune responses ↗

Location: Cytosolic sensors of pathogen-associated DNA

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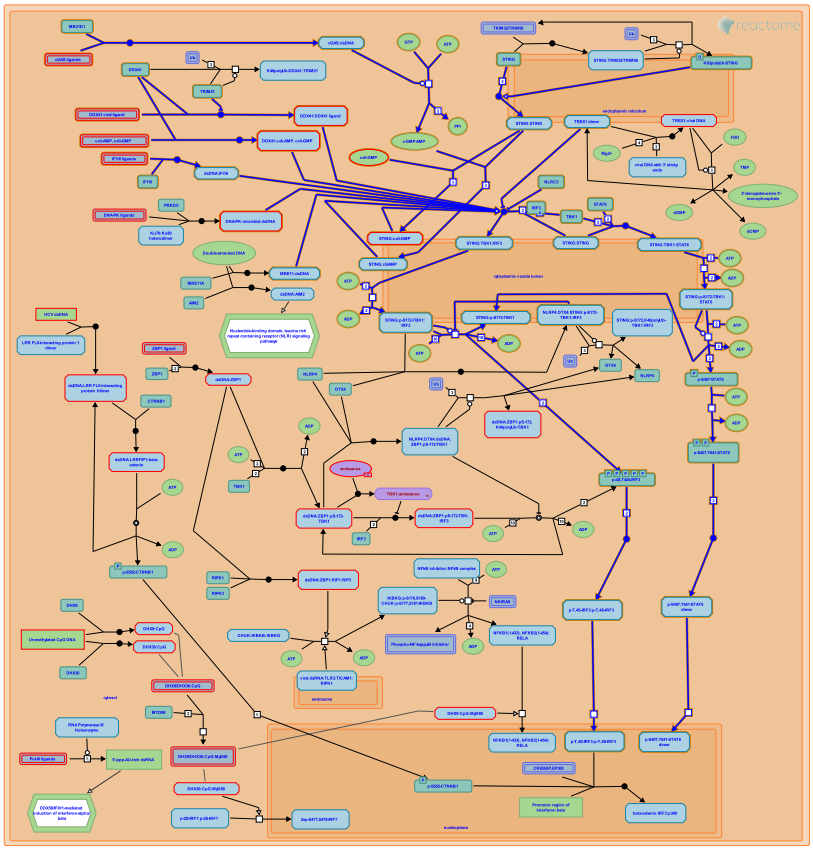

STING (stimulator of IFN genes; also known as MITA/ERIS/MPYS/TMEM173) is an endoplasmic reticulum (ER) resident, which is required for effective type I IFN production in response to nucleic acids. Indeed, select pathogen-derived DNA or RNA were shown to activate STING in human and mouse cells (Ishikawa H and Barber GN 2008; Ishikawa H et al. 2009; Sun W et al. 2009; Prantner D et al. 2010). Importantly, in vitro studies have shown that STING is essential for Mycobacterium tuberculosis (Manzanillo PS et al. 2012), Plasmodium falciparum (Sharma S et al. 2011) and human immunodeficiency virus (HIV) induced type I IFN production [Yan N et al 2010]. Mycobacterium tuberculosis, plasmodium falciparum and HIV are three deadliest pathogens, which kill millions of people each year worldwide.

STING has been also implicated in type I IFN response which was stimulated by fusion of viral and target-cell membrane in a manner independent of DNA, RNA and viral capsid [Holm CK et al 2012].

Under steady state conditions, STING is positioned at the translocon complex within the ER membrane. However upon stimulation with intracellular DNA it translocates from ER to perinuclear vesicles via the Golgi by mechanisms that remain unclear (Ishikawa H and Barber GN 2008; Sun W et al. 2009; Ishikawa H et al. 2009; Saitoh T et al. 2009). Mouse Sting trafficking in dsDNA-stimulated mouse embryonic fibroblasts (MEF) cells was found to depend on autophagy-related gene 9a (Atg9a) (Saitoh T et al. 2009).

STING was reported to function as a signaling adaptor or coreceptor in response to cytosolic dsDNA (Unterholzner L et al. 2010; Zhang Z et al. 2011). STING was also shown to function as a direct DNA sensor to induce the innate immune response in human telomerase fibroblasts (hTERT-BJ1) and murine embryonic fibroblasts (MEFs) (Abe T et al. 2013). Additionally, STING is thought to function as a direct sensor of cyclic dinucleotides. STING was shown to interact directly with c-di-GMP in human embryonic kidney HEK293T cell lysates (Burdette DL et al. 2011). Once STING is stimulated, its C-terminus serves as a signaling scaffold to recruit IRF3 and TBK1, which leads to TBK1-dependent phosphorylation of IRF3 (Tanaka Y and Chen ZJ 2012).

Mouse, but not human STING, can also bind vascular disrupting agents 5,6-dimethylxanthenone-4-acetic acid (DMXAA) and the antiviral small molecule 10-carboxymethyl-9-acridanone (CMA) to induce type I IFN production, suggesting a species-specific drug effect on the STING-mediated host response (Conlon J et al. 2013; Cavlar T et al. 2013).

Literature references

Cox, JS., Manzanillo, PS., Shiloh, MU., Portnoy, DA. (2012). Mycobacterium tuberculosis activates the DNA-dependent cytosolic surveillance pathway within macrophages. *Cell Host Microbe, 11*, 469-80. ↗

Konno, H., Ahn, J., Harashima, A., Morales, A., Xia, T., Abe, T. et al. (2013). STING Recognition of Cytoplasmic DNA Instigates Cellular Defense. *Mol. Cell, 50*, 5-15. ↗

Chen, D., Chen, H., Zhou, X., Zhou, Y., Zhai, Z., Jiang, Z. et al. (2009). ERIS, an endoplasmic reticulum IFN stimulator, activates innate immune signaling through dimerization. *Proc. Natl. Acad. Sci. U.S.A., 106*, 8653-8. ↗

Ablasser, A., Hopfner, KP., Cavlar, T., Hornung, V., Deimling, T. (2013). Species-specific detection of the antiviral small-molecule compound CMA by STING. *EMBO J., 32*, 1440-50. ↗

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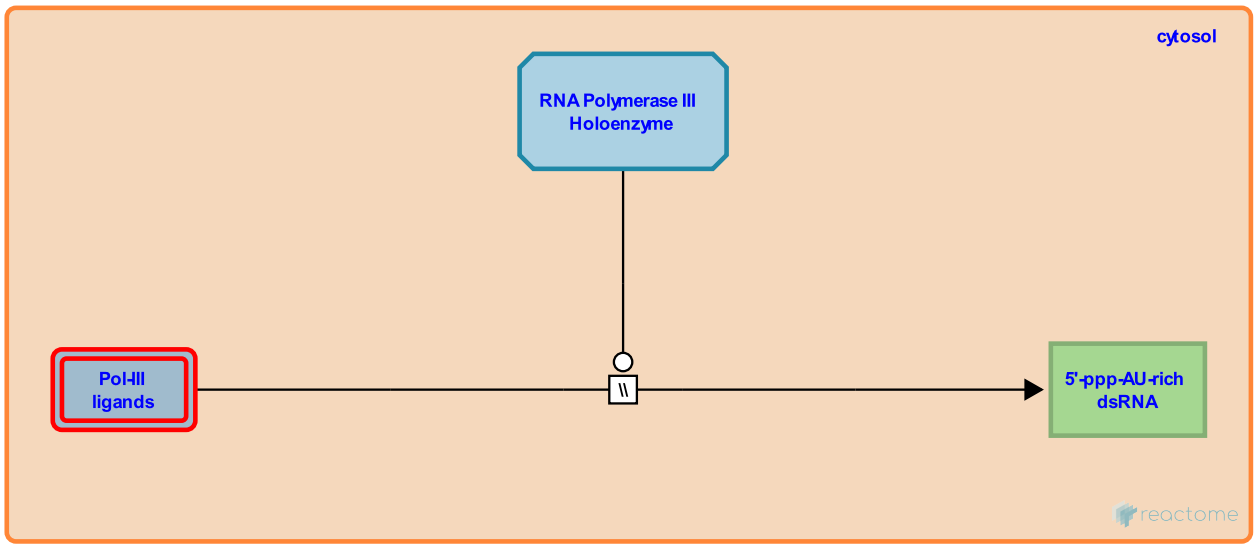
RNA polymerase III transcribes microbial dsDNA to dsRNA ↗

Location: Cytosolic sensors of pathogen-associated DNA

Stable identifier: R-HSA-1964482

Type: omitted

Compartments: cytosol



RNA polymerase III (POL III) was reported to sense and transcribe cytosolic AT-rich dsDNA into 5'-triphosphate poly(A-U) RNA in human and mouse cells. This dsRNA ligand in turn activated retinoic acid-inducible gene I (RIG-I) leading to production of type I interferon and activation of the transcription factor NF-kappaB (Chiu YH et al. 2009, Ablasser A et al. 2009). Knockdown of POL III expression by siRNA or inhibition of its enzymatic activity by specific chemical inhibitor ML-60218 prevented IFN beta induction in HEK293 cells stimulated with DNA viruses or poly(dA-dT) (Chiu YH et al. 2009, Ablasser A et al. 2009). Moreover, Pol-III inhibition blocked interferon induction by intracellular Legionella pneumophila bacteria [Chiu YH et al 2009].

This project represents cytosolic RNA polymerase III as a complex comprising 17 subunits, although the precise biochemical composition of the cytosolic holoenzyme complex which specifically recognizes AT-rich DNA is not yet known.

Literature references

Chiu, YH., Chen, ZJ., Macmillan, JB. (2009). RNA polymerase III detects cytosolic DNA and induces type I interferons through the RIG-I pathway. *Cell, 138*, 576-91. ↗

Fitzgerald, KA., Ablasser, A., Bauernfeind, FG., Hornung, V., Latz, E., Hartmann, G. (2009). RIG-I-dependent sensing of poly(dA:dT) through the induction of an RNA polymerase III-transcribed RNA intermediate. *Nat Immunol, 10*, 1065-72. ↗

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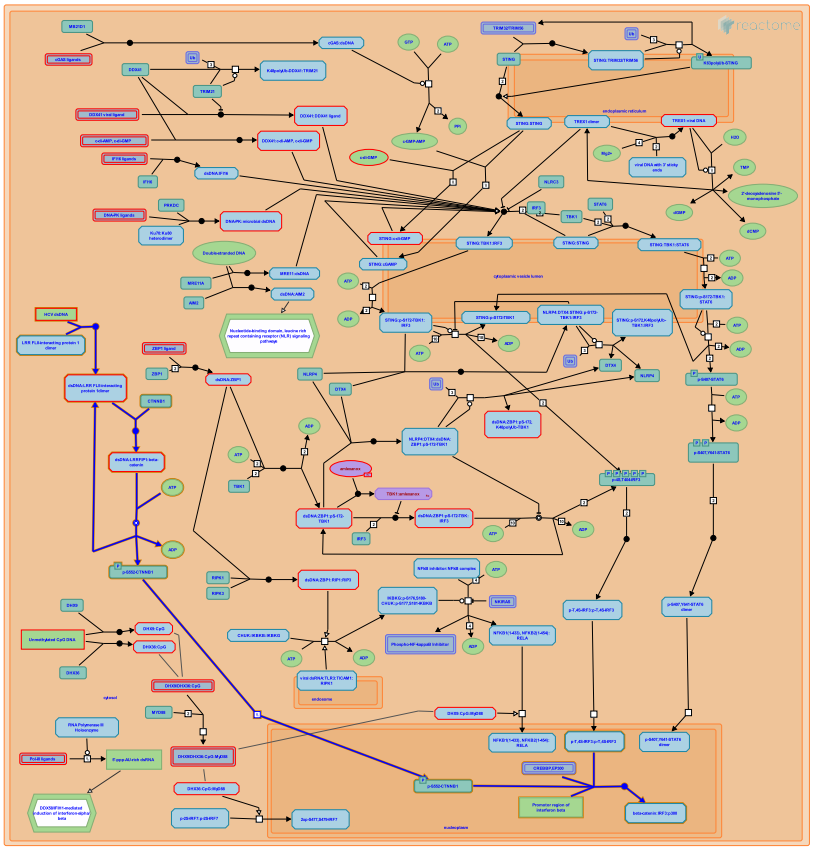
LRR FLII-interacting protein 1 (LRRFIP1) activates type I IFN production ↗

Location: Cytosolic sensors of pathogen-associated DNA

Stable identifier: R-HSA-3134973



Leucine-rich repeat flightless-interacting protein 1 (LRRFIP1) can bind exogenous double-stranded RNA and double-stranded DNA (Wilson SA et al. 1998; Yang P et al. 2010). LRRFIP1 was shown to mediate Listeria monocytogenes- and vesicular stomatitis virus (VSV)-induced IFN-beta production in mouse primary macrophages by regulating beta-catenin activity. Beta-catenin possibly functions as a transcriptional cofactor of IRF3 to initiate Ifnb1 transcription (Yang P et al. 2010).

Literature references

Wilson, SA., Kingsman, AJ., Brown, EC., Kingsman, SM. (1998). TRIP: a novel double stranded RNA binding protein which interacts with the leucine rich repeat of flightless I. *Nucleic Acids Res., 26*, 3460-7. ↗

Wen, M., Rui, Y., Liu, X., Yang, P., Cao, X., Zheng, Y. et al. (2010). The cytosolic nucleic acid sensor LRRFIP1 mediates the production of type I interferon via a beta-catenin-dependent pathway. *Nat. Immunol., 11*, 487-94. ↗

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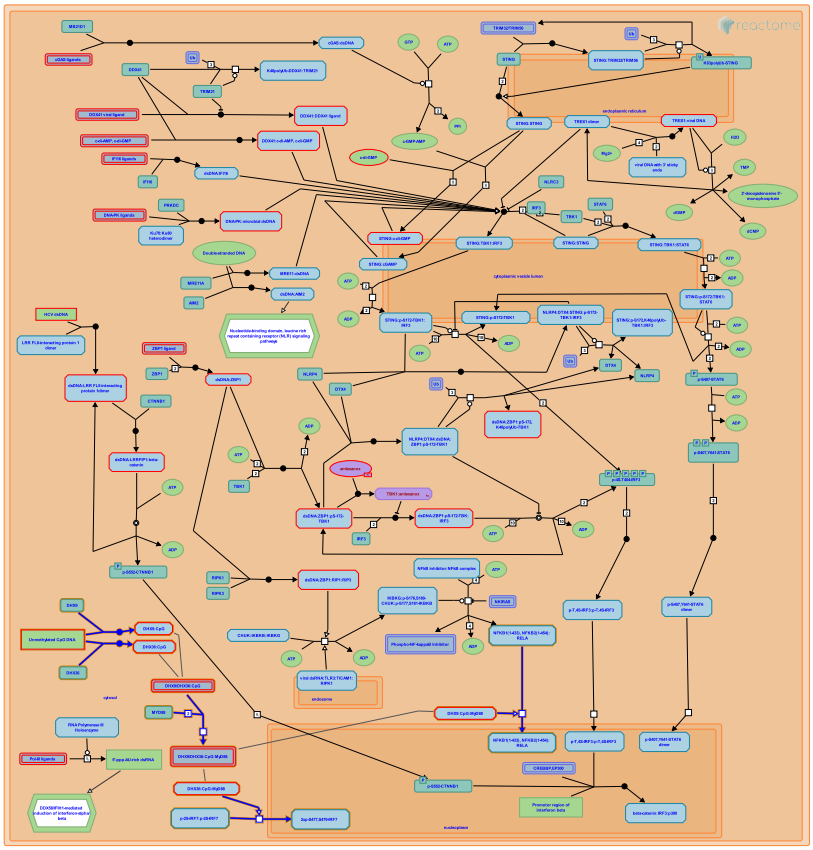
DEx/H-box helicases activate type I IFN and inflammatory cytokines production ↗

Location: Cytosolic sensors of pathogen-associated DNA

Stable identifier: R-HSA-3134963



DHX36 and DHX9 are aspartate-glutamate-any amino acid aspartate/histidine (DExD/H) box helicase (DHX) proteins that localize in the cytosol. The DHX RNA helicases family includes a large number of proteins that are implicated in RNA metabolism. Members of this family, RIG-1 and MDA5, have been shown to sense a non-self RNA leading to type I IFN production. RNA helicases DHX36 and DHX9 were found to trigger host responses to non-self DNA in MyD88-dependent manner. DHX36 sensed CpG class A, while DHX9 sensed CpG class B. Both DHX36 and DHX9 were critical for antiviral immune responses in viral DNA-stimulated human plasmacytoid dendritic cells (pDC) (Kim T et al. 2010).

Literature references

Hanabuchi, S., Plumas, J., Pazhoor, S., Bover, L., Kim, T., Facchinetti, V. et al. (2010). Aspartate-glutamate-alanine-histidine box motif (DEAH)/RNA helicase A helicases sense microbial DNA in human plasmacytoid dendritic cells. *Proc. Natl. Acad. Sci. U.S.A., 107*, 15181-6. ↗

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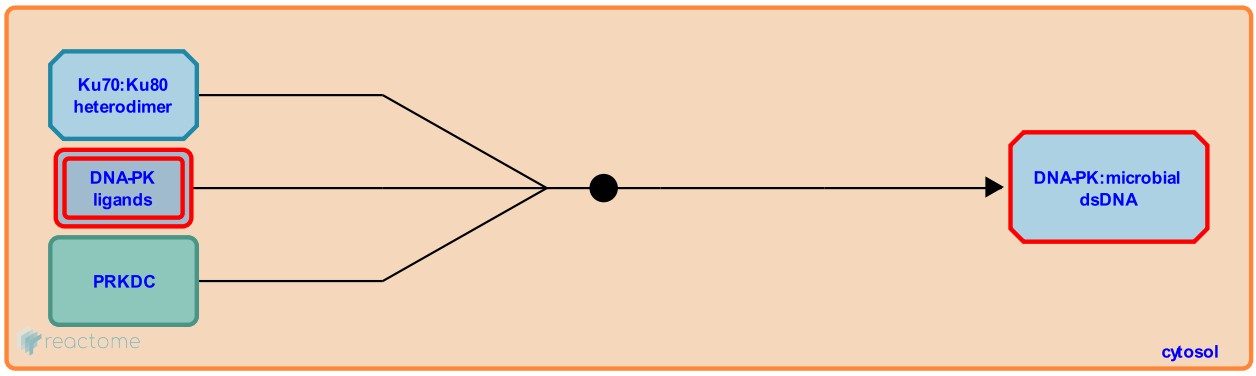
DNA-PK binds microbial dsDNA ↗

Location: Cytosolic sensors of pathogen-associated DNA

Stable identifier: R-HSA-3134821

Type: binding

Compartments: cytosol



DNA-dependent serine/threonine protein kinase DNA-PK is a DNA damage sensor, which is composed of a large catalytic subunit DNA-PKcs and a heterodimer of Ku70 & Ku80 subunits. DNA-PK was found both in the nucleus and in the cytosol (Lucero H et al. 2003). While in the nucleus DNA-PK is critical for the repair of double-stranded DNA breaks during the lymphocyte development, in the cytosol it can also bind DNA fragments to transmit stress signals (Dip R & Naegeli H 2005; Yotsumoto S et al. 2008; Dragoi AM et al. 2004; Ferguson BJ et al. 2012).

This Reactome event presents DNA-PK as a holoenzyme, however it remains unclear whether all DNA-PK subunits are critical for exogenous DNA recognition, whether they function as a DNA-PK complex or each subunit acts independently in certain circumstances (Zhang X et al. 2011; Ferguson BJ et al. 2012).

Studies involving different human and mouse cell lines yielded variable results regarding to DNA-PK signaling functions. The catalytic subunit DNA-PKcs has been shown to associate with Akt upon CpG-OND-stimulation triggering transient nuclear translocation of Akt in mouse bone marrow-derived macrophages (BMDMs)(Dragoi AM et al. 2004). DNA-PKcs has been also reported to induce ERK activation and production of anti-inflammatory cytokine IL-10 in CpG-ODN-stimulated mouse monocyte/macrophage cell line RAW264.7, while production of pro-inflammatory cytokine IL-12 was negatively regulated (Yotsumoto S et al. 2008). In addition, endosomal translocation of CpG-ODN was found to regulate DNA-PKcs-mediated responses to CpG-OND (Yotsumoto S et al. 2008; Hazeki K et al. 2011). Moreover, DNA-PK subunits have been implicated in IFN regulatory factor (IRF)-dependent innate immune responses. Ku-70 was shown to induce production of type III IFN (IFN -lamda 1) in human embryonic kidney HEK293 cells transfected with DNA. The Ku70-mediated IFN-lamda 1 activation required a longer size of DNA (>500 bp DNA) (Zhang X et al. 2011). Whether DNA-PK mediates activation of IFN-beta production is debatable. Ku70- or DNA-PKcs-deficient mouse bone marrow-derived macrophages cells mounted an identical IFN-beta response when compared to their wild-type controls (Stetson DB & Medzhitov R 2006). However, the other group demonstrated that DNA-PK induced IRF3-dependent production of IFN-beta in DNA-stimulated mouse embryonic fibroblast(MEF) and human HEK293 cells (Ferguson BJ et al. 2012). Thus, the molecular mechanism behind DNA-PK activation by cytosolic DNA remains to be clarified.

It's interesting to note that in the nucleus DNA-PK may regulate IRF3 transcriptional activity in response to viral infection. DNA-PK was found to bind and phosphorylate IRF-3 at Thr-135 in Sendai virus (SV)-treated human endometrial adenocarcinoma HEC1B cells. DNA-PK-dependent phosphorylation at Thr-135 is thought to retain transcriptionally active IRF-3 in the nucleus (Karpova AY et al. 2002).

Literature references

Imamichi, T., Lane, HC., Lidie, KB., Huang, DW., Baseler, MW., Yang, J. et al. (2011). Cutting edge: Ku70 is a novel cytosolic DNA sensor that induces type III rather than type I IFN. *J. Immunol., 186*, 4541-5. ↗

Peters, NE., Ferguson, BJ., Ren, H., Smith, GL., Mansur, DS. (2012). DNA-PK is a DNA sensor for IRF-3-dependent innate immunity. *elife, 1*, e00047. ↗

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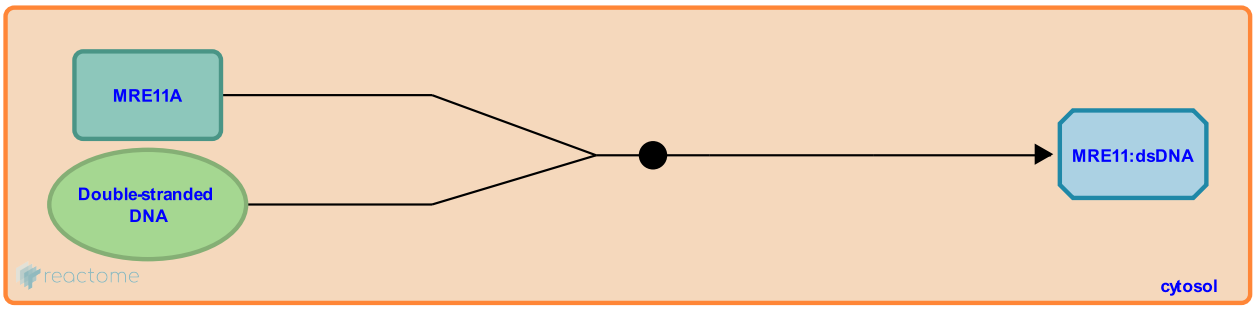
MRE11 binds cytosolic DNA ↗

Location: Cytosolic sensors of pathogen-associated DNA

Stable identifier: R-HSA-3204303

Type: binding

Compartments: cytosol



DNA damage sensor, meiotic recombination 11 homolog A (MRE11) has been shown to function as a cytosolic sensor of dsDNA. The observations that MRE11 mediates recognition of dsDNA rather than pathogens suggest that the biological significance of MRE11-mediated intracellular DNA recognition is to respond to damaged host cells, rather than defense against foreign pathogens (Kondo T et al. 2013). Cells with a mutation of MRE11 gene derived from a patient with ataxia-telangiectasia-like disorder, and cells in which Mre11 was knocked down, had defects in dsDNA-induced type I IFN production (Kondo T et al. 2013).

Literature references

Kawai, T., Ishii, KJ., Akira, S., Kobayashi, J., Barber, GN., Saitoh, T. et al. (2013). DNA damage sensor MRE11 recognizes cytosolic double-stranded DNA and induces type I interferon by regulating STING trafficking. *Proc. Natl. Acad. Sci. U.S.A., 110*, 2969-74. ↗

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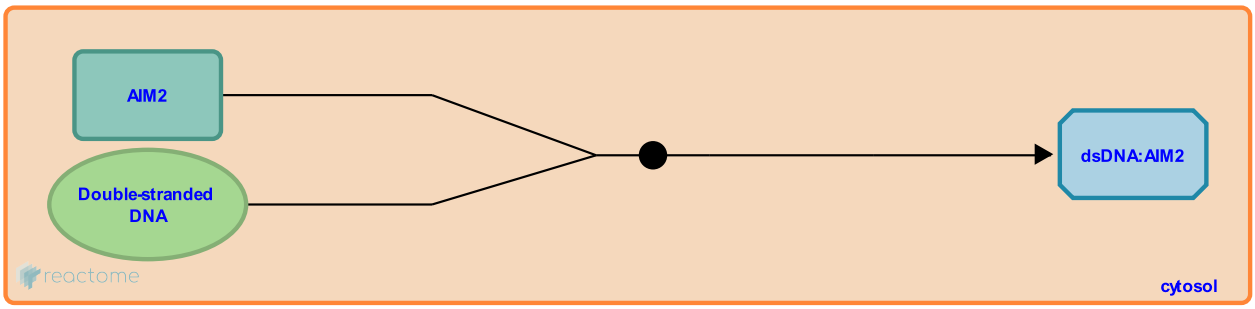
AIM2 binds dsDNA ↗

Location: Cytosolic sensors of pathogen-associated DNA

Stable identifier: R-HSA-844619

Type: binding

Compartments: cytosol



AIM2 binds to cytosolic dsDNA via its C-terminal HIN domain. The source of the dsDNA can be can be viral, bacterial or derived from the host (Hornung et al. 2009, Muruve et al. 2008). Multiple AIM2 molecules may bind the same dsDNA (Fernandes-Alnemri et al. 2008).

Literature references

Horvath, G., Fitzgerald, KA., Ablasser, A., Bauernfeind, FG., Latz, E., Hornung, V. et al. (2009). AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC. *Nature, 458*, 514-8. ↗

Wu, J., Datta, P., Alnemri, ES., Yu, JW., Fernandes-Alnemri, T. (2009). AIM2 activates the inflammasome and cell death in response to cytoplasmic DNA. *Nature, 458*, 509-13. ↗

Burckstummer, T., Colinge, J., Superti-Furga, G., Bilban, M., Dixit, E., Bennett, KL. et al. (2009). An orthogonal proteomic-genomic screen identifies AIM2 as a cytoplasmic DNA sensor for the inflammasome. *Nat Immunol, 10*, 266-72. ↗

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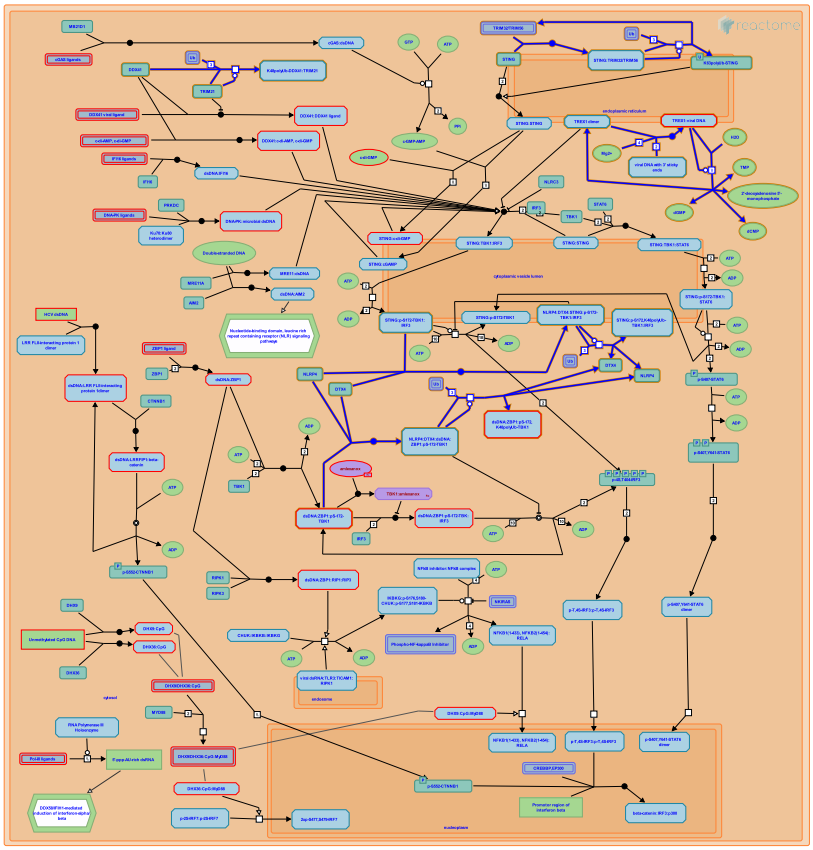
Regulation of innate immune responses to cytosolic DNA ↗

Location: Cytosolic sensors of pathogen-associated DNA

Stable identifier: R-HSA-3134975



Innate immune responses are coordinated and regulated to provide an efficient first line of defense against pathogens and at the same time to prevent host self-damage. Here we present some regulatory events involved in the detection of cytosolic nucleic acids.

Literature references

Savitsky, D., Tamura, T., Yanai, H., Taniguchi, T. (2009). Regulation of the cytosolic DNA-sensing system in innate immunity: a current view. *Curr. Opin. Immunol., 21*, 17-22. ↗

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